Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials

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Summary

Background Few trials of adjuvant breast radiotherapy have incorporated patient-reported breast symptoms and related areas of quality of life. We assessed these measures in a quality-of-life study that was part of the randomised START (Standardisation of Breast Radiotherapy) trials.

Methods In START trial A, 2236 patients were randomly assigned to receive either 39 Gy or 41·6 Gy delivered in 13 fractions over 5 weeks or a global standard of 50 Gy in 25 fractions. In START trial B, 2215 women were randomly assigned to receive either 40 Gy in 15 fractions over 3 weeks or the same control regimen (50 Gy in 25 fractions) as in trial A. 2739 patients were eligible for the quality-of-life study of whom 2208 (81%) were accrued (1129 patients from trial A and 1079 from trial B). Participants completed the EORTC QLQ-C30 and BR23 questionnaires and protocol-specific radiotherapy items up to 5 years after radiotherapy. We compared results across regimens with generalised estimating equations and survival analyses. The START trials are registered, ISRCTN59368779.

Findings At 5 years, up to 40% women reported moderate or marked changes to the breast after radiotherapy, and arm and shoulder pain affected up to a third of patients. Breast symptoms and body image concerns reduced over time. Rates of radiotherapy adverse effects were lower for the 39 Gy regimen in trial A and the 40 Gy regimen in trial B, compared with the 50 Gy control regimen; rates of radiotherapy adverse effects were similar between the 41·6 Gy and 50 Gy regimens in trial A. Adverse change in skin appearance was significantly lower for patients who received 39 Gy compared with those who received 50 Gy (HR 0·63, 95% CI 0·47–0·84) and for those who received 40 Gy compared with those who received 50 Gy (0·76, 0·60–0·97); no significant difference was observed between patients who received 41·6 Gy and those who received 50 Gy in trial A (0·83, 0·63–1·08). Patient self-ratings of breast symptoms discriminated a 10% difference in randomised dose intensity. Up to a third of women reported moderate or marked pain in the arm and shoulder over 5 years whilst more than 10% experienced moderate or marked arm and hand swelling, with no significant difference in arm/shoulder subscale scores between the regimens in trial A or trial B; many baseline arm and shoulder symptoms were associated with prior surgery.

Interpretation A substantial proportion of women report moderate or marked breast, arm, and shoulder symptoms over 5 years of follow-up after radiotherapy, but with no detriment to body image. Nonetheless, most patients stand to gain from hypofractionated radiotherapy regimens with a potential for fewer adverse effects; this strengthens the evidence from the START trials for hypofractionated regimens for women requiring radiotherapy for early breast cancer.

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Introduction

The safety and effectiveness of radiotherapy schedules that deliver a lower total dose in fewer, larger fractions than the international standard regimen has long been uncertain, despite widespread use in early breast cancer. In the UK, two randomised trials (Standardisation of Breast Radiotherapy [START] trials A and B) were run concurrently to compare the international standard dose (50 Gy delivered in 25 fractions over 5 weeks) with alternative schedules based on fewer larger fractions. In trial A,[1] doses of 39 Gy and 41·6 Gy given in 13 fractions over 5 weeks were compared with the standard international regimen. Trial B[2] was a pragmatic non-inferiority trial comparing the same standard dose with 40 Gy in 15 fractions over 3 weeks, a commonly used regimen in the UK. The results of trial A showed that rates of late-occurring adverse effects assessed from photographs were significantly lower for the 39 Gy regimen compared with the 50 Gy control. The 41·6 Gy regimen was similar to 50 Gy in terms of radiotherapy adverse effects and local tumour control.[1] In trial B, for the 40 Gy regimen, local tumour control was at least as good as with 50 Gy, and late adverse effects were reduced.[2]

Regimens with shorter schedules could have a positive effect on radiotherapy resource use and patients' convenience. However, over the years, concerns about lengthy treatments might have contributed to women's choice of mastectomy alone over breast-conserving surgery plus radiotherapy,[3] while age and geographic location have

also been cited as predictors of mastectomy.[4] This situation is not desirable, since good-to-excellent breast cosmesis for most patients has been reported after breast-conserving surgery and a range of radiotherapy schedules,[5–8] albeit with variable levels of functional morbidity.[9,10]

In a pilot study to the START trials, photographic assessments showed that a third of women had some change in breast appearance over 10 years of follow-up, with evidence of variation according to fractionation regimen over time.[11] Rates of marked radiation effects assessed from photographs were significantly higher for patients allocated a 42·9 Gy regimen delivered in 13 fractions compared with 50 Gy in 25 fractions, with lowest rates for 39 Gy in 13 fractions (although not statistically significant). However, patient's ratings of the effect of radiotherapy on cosmesis and breast, arm, and shoulder symptoms were not recorded in the pilot study and are generally poorly documented in published work.[3,12]

The START trials built on the experience of the pilot study by making a minor adjustment to one of the radiotherapy doses for use in trial A and by including a detailed quality-of-life study in trials A and B.[1,2] Here, using data from each trial separately, we compare radiotherapy schedules with respect to patients' self-assessments of normal tissue effects on the basis of changes in breast, arm, shoulder symptoms and function, and body image over 5 years of follow-up.

Methods

Patients

Participation in the START trials quality-of-life study was open to all radiotherapy centres recruiting patients to the START trials, for which full details of patients and procedures have been published.[1,2] Women with early-stage invasive breast cancer needing radiotherapy after primary surgery were eligible for the START trials if they were older than 18 years, did not have breast reconstruction before radiotherapy, and were available for follow-up. All centres could choose at the outset whether or not to participate in the quality-of-life study, with the expectation that all patients in participant centres would be approached for the quality-of-life study. No differences were recorded in terms of radiotherapy planning and delivery between centres opting in and out of the quality-of-life study (data not shown). The START trials included a rigorous radiotherapy quality-assurance programme, which ensured that the START protocol was adhered to at all centres.

We reached accrual targets for the quality-of-life study much earlier than expected, so we decided to continue beyond the target sample size to boost precision of estimates and to make the most of the opportunity to accumulate a unique dataset. Trial B completed accrual ahead of trial A. In the last year of recruitment we focused accrual in the quality-of-life study on specific subgroups—those who had undergone mastectomy, had received chemotherapy or were intended to have lymph-node irradiation in trial A, and those who were intended to have lymph-node irradiation in trial B.

The South Thames Multi-Research Ethics Committee approved the START trials in September, 1998, and the local ethics committees of all participating centres also gave approval. We obtained written informed consent for all patients. The Cancer Research UK's Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton, UK, coordinated the START Trials. Full details of the organisational aspects of the trials have been published previously.[1,2]

Procedures

Women in START trial A were randomly assigned to radiotherapy over a 5-week period at either 50 Gy in 25 fractions of 2·0 Gy (control) or 41·6 Gy in 13 fractions of 3·2 Gy or 39 Gy in 13 fractions of 3·0 Gy.[1] Treatment entailed five fractions per week in the control group and five treatments every 2 weeks in each of the 13 fraction schedules (three fractions one week and two the next). In trial B, patients were randomly allocated radiotherapy at either 50 Gy in 25 fractions of 2·0 Gy over 5 weeks (control) or 40 Gy in 15 fractions of 2·67 Gy over 3 weeks (ie, five fractions per week for both schedules).[2] Randomisation was done via telephone at ICR-CTSU. Treatment allocation could not be masked because of the different daily schedules of the radiotherapy regimens. Computer-generated random permuted blocks were used as the method of allocation, with patients stratified by hospital, type of surgery (breast-conserving surgery or mastectomy), and intention to give a tumour-bed boost or not. At least 2 weeks was needed between exposure to chemotherapy and radiotherapy, and a radiotherapy boost to the tumour bed was prescribed according to local policy. Full details of the radiotherapy planning and treatment are presented elsewhere.[1,2]

Patients who consented to participate in the quality-of-life study completed a questionnaire booklet in the breast clinic before randomisation. We mailed subsequent questionnaires for completion at home at 6, 12, 24, and 60 months post-randomisation (after checking the individual's current health status with their hospital team or family doctor). We prompted patients by telephone or letter if questionnaires were not returned within 3 weeks. Full details of the quality-of-life study are available elsewhere.[13]

We assessed quality of life with the EORTC (European Organisation for Research and Treatment of Cancer) general cancer scale QLQ-C30[14] and breast-cancer module (BR23).[15] Both measures use a four-point response format for individual items (not at all, a little, quite a bit, very much). BR23 consists of six subscales, of which three were used in the analysis: breast symptoms subscale (four items [pain, swelling, oversensitivity, and skin problems in the breast]), arm subscale (three items [swelling in arm or hand, arm or shoulder pain, and difficulty moving the arm]), and body image (four items). Other functioning and symptom subscales and items of

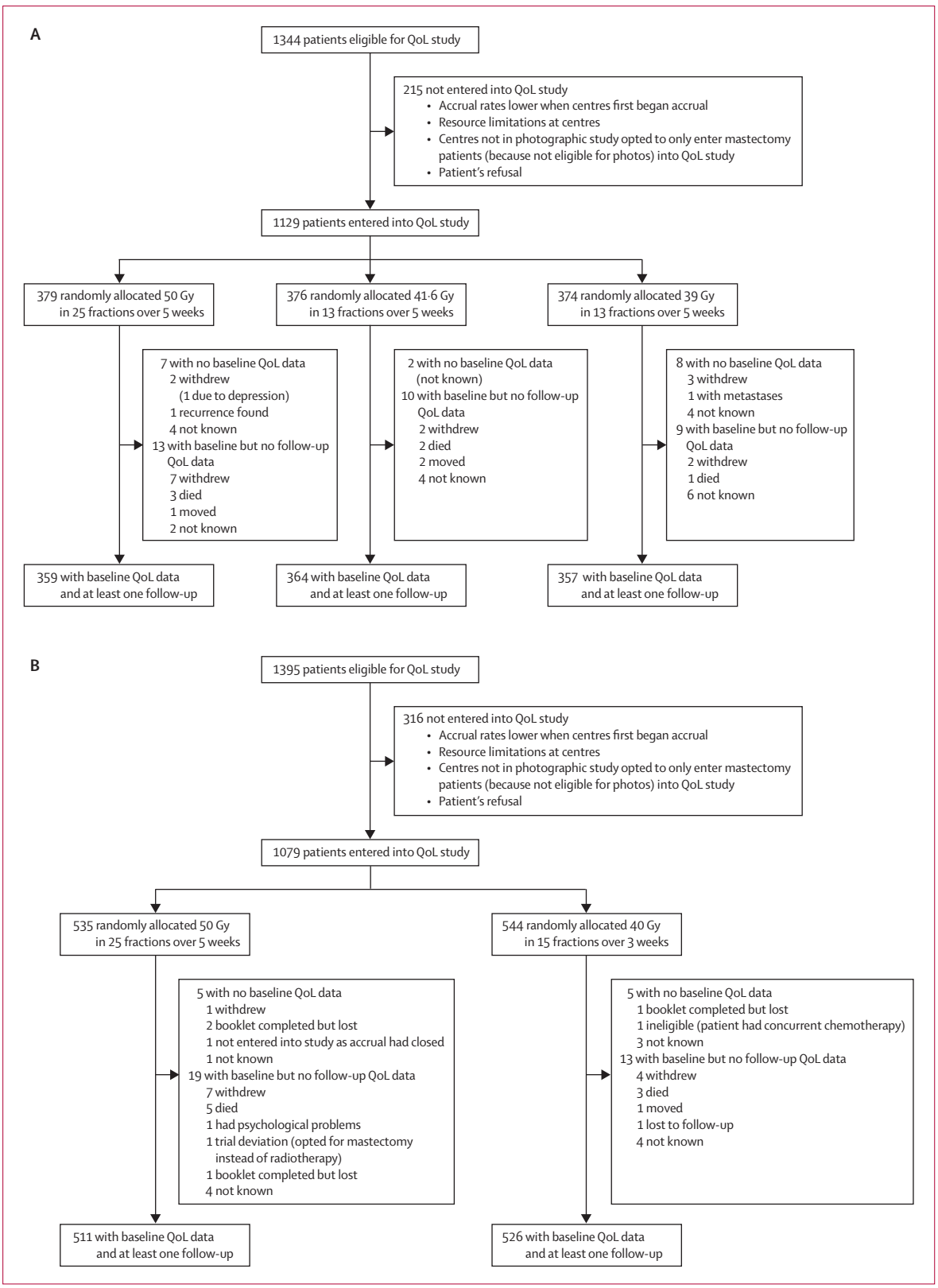

Figure 1: **Trial profiles of patients from START trial A (A) and trial B (B) quality-of-life study**

	Trial A (n=1129)	Trial B (n=1079)
Age (years)*	57·0 (10·8)	56·7 (10·0)
Type of surgery		
Breast-conserving surgery	885 (78%)	946 (88%)
Mastectomy	244 (22%)	133 (12%)
Time since surgery (weeks)†	9·3 (5·7–21·6)	8·1 (5·3–17·6)
Adjuvant systemic therapy		
None	93 (8%)	35 (3%)
Chemotherapy only	109 (10%)	115 (11%)
Tamoxifen only	577 (51%)	689 (64%)
Chemotherapy and tamoxifen	318 (28%)	219 (20%)
Other	25 (2%)	17 (2%)
Unknown	7 (1%)	4 (<1%)
Pathological node status		
Positive	379 (34%)	313 (29%)
Negative	723 (64%)	728 (67%)
Unknown	27 (2%)	38 (4%)
Boost (breast-conserving surgery patients only)		
Yes	628 (71%)	481 (51%)
No	250 (28%)	455 (48%)
Unknown	7 (1%)	10 (1%)
Pathological tumour size (cm)†	2 (1·4–2·7)	1·7 (1·2–2·3)
Tumour size distribution		
<1	41 (4%)	141 (13%)
1 to <2	507 (45%)	500 (46%)
2 to <3	312 (28%)	306 (28%)
≥3	263 (23%)	127 (12%)
Unknown	6 (<1%)	5 (<1%)
Tumour grade		
1	230 (20%)	286 (27%)
2	546 (48%)	484 (45%)
3	329 (29%)	283 (26%)
Unknown	24 (2%)	26 (2%)
Lymphatic radiotherapy		
Yes	262 (23%)	103 (10%)
No	861 (76%)	965 (89%)
Unknown	6 (1%)	11 (1%)
Axillary surgery		
Yes	1102 (98%)	1042 (97%)
No	27 (2%)	37 (3%)
Breast size (from photographs)		
Small	91 (8%)	79 (7%)
Medium	631 (56%)	668 (62%)
Large	119 (11%)	144 (13%)
Unknown	37 (3%)	45 (4%)
Not in photographic study	251 (22%)	143 (13%)
Surgical deficit (from photographs)		
Small	495 (44%)	510 (47%)
Medium	271 (24%)	299 (28%)
Large	75 (7%)	82 (8%)
Unknown	37 (3%)	45 (4%)
Not in photographic study	251 (22%)	143 (13%)

Data are number (%) unless stated otherwise. *Data are mean (SD). †Data are median (IQR).

Table 1: **Characteristics of patients included in quality-of-life study**

the BR23 and QLQ-C30 are outside the aim of this analysis and are not presented here.

We constructed protocol-specific items to assess particular post-radiotherapy effects on normal tissues (not covered in the EORTC quality-of-life scales), with the same four-point response format as the EORTC measures. These items included change in skin appearance in the area of the affected breast (to account for telangiectasia and other effects), overall change in breast appearance (to account for asymmetry and distortion), firmness to touch of the affected breast (to account for fibrosis), and reduction in size of the affected breast (to account for shrinkage); the last three items only applied to patients who had completed breast-conserving surgery. Cronbach's alpha coefficient for these four post-radiotherapy items was 0·72, indicating satisfactory internal consistency. An additional item assessed shoulder stiffness.

We assessed body image with a validated, cancer-specific, ten-item scale (body image scale),[16] which includes the BR23 body image subscale. Again, the same four-point response format as the EORTC measures was used. Items included change in self-consciousness with appearance, feeling less physically attractive, less sexually attractive, less feminine, dissatisfaction with appearance when dressed, dissatisfaction with body or scars, body feeling less whole, difficulty looking at self naked, and avoidance of people because of appearance. We included the ten-item body image scale in this analysis.

Statistical analysis

We estimated that a minimum of 200 patients per radiotherapy schedule would be needed to compare quality-of-life endpoints. This number would allow estimation of the proportion of patients with a particular side-effect or specified degree of morbidity on a quality-of-life domain with a precision of at least 7% (maximum SE 3·5%), and it would enable detection of differences between every test regimen and the control schedule of at least 20% (with 90% power and α=0·01, allowing for testing of multiple endpoints). We included an allowance of 10% to account for non-completion of questionnaires due to illness, death, or non-compliance.

For analyses, a baseline and at least one follow-up assessment were needed. We categorised questionnaire item scores for BR23 and protocol items according to whether or not a patient had ever recorded an item as "quite a bit" or "very much", corresponding to moderate or marked effects. We then used survival analysis to measure time to first reporting of a moderate or marked event, using the date of completion of the questionnaire to calculate length of follow-up from randomisation. We calculated Kaplan-Meier estimates of 5-year rates, along with hazard ratios obtained from Cox's proportional-hazards regression analysis (with 95% CI). For symptoms that were included in the baseline questionnaire, the Cox's proportional-hazards regression model included a term for the baseline score. We tested radiation dose

response by direct comparison of the 41·6 Gy and 39 Gy regimens in trial A.

For continuous symptom scores (breast and arm symptoms, body image), we summarised distributions at every timepoint according to radiotherapy regimen with medians and IQR, since data were skewed and no suitable transformation could be found. We compared subscale scores for breast and arm symptoms and body image scale summary scores over the 5 years of follow-up and between radiotherapy regimens with generalised estimating equations, which allow for correlation within repeated observations per individual.[17]

Since patients were stratified at randomisation by type of primary surgery and intention to give a radiotherapy boost to the tumour bed, we undertook stratified analyses and tests for interaction to see whether the relative effects of the radiotherapy regimens varied according to these subgroups. For the continuous subscales of breast and arm symptoms and body image, stratified analyses included all follow-up data in the generalised estimating equation models, but only 5-year data are presented for simplicity. We also did a secondary analysis of arm, shoulder, and hand symptoms, with adjustment for axillary surgery and lymphatic radiotherapy, but since this modification made almost no difference to the treatment effects, unadjusted results are presented.

We undertook all analyses with SPSS version 15.0. Analysis was on an intention-to-treat basis, which is appropriate for assessment of safety in a trial in which compliance with allocated treatment is high (2175 of 2208 [99%] patients in the quality-of-life study received their allocated radiotherapy regimen) because underestimation of adverse risks is not a concern. The START trials are registered, number ISRCTN59368779.

Role of the funding source

The funding sources provided peer-reviewed approval for the trials and were observers on the Trial Steering Committee, but had no other role in the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between January, 1999, and December, 2002, 4451 women were enrolled into the START trials (2236 from 17 centres in trial A and 2215 from 23 centres in trial B). Of these, 2208 patients were accrued into the quality-of-life study, with 1129 from 13 centres in trial A and 1079 from 21 centres in trial B (figure 1). The proportion of every centre's trial patients entered into the quality-of life-study varied. Reasons for non-accrual were not obtained on an individual basis; at some centres, non-accrual was due to resource limitations, and at others, patients who had completed breast-conserving surgery were not recruited into the quality-of-life study if centres did not have the facilities to participate in the photographic assessment study. Over the whole accrual period, the median proportion per centre of trial patients entered into the quality-of-life study out of those eligible was 91% (IQR 75–97).

	0 months	6 months	12 months	24 months	60 months
BR23 breast symptoms subscale (0–100)					
Trial A					
50 Gy	16·7 (8·3–25·0)	16·7 (8·3–33·3)	16·7 (8·3–25·0)	8·3 (0–25·0)	8·3 (0–25·0)
41·6 Gy	16·7 (8·3–25·0)	16·7 (8·3–33·3)	16·7 (0–25·0)	8·3 (0–25·0)	8·3 (0–16·7)
39 Gy	16·7 (8·3–25·0)	16·7 (8·3–25·0)	16·7 (0–25·0)	8·3 (0–16·7)	8·3 (0–16·7)
Trial B					
50 Gy	16·7 (8·3–25·0)	16·7 (8·3–33·3)	16·7 (8·3–25·0)	8·3 (0–16·7)	8·3 (0–16·7)
40 Gy	16·7 (8·3–25·0)	16·7 (8·3–33·3)	16·7 (0–25·0)	8·3 (0–16·7)	8·3 (0–16·7)
BR23 arm or shoulder symptoms subscale (0–100)					
Trial A					
50 Gy	22·2 (0–33·3)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
41·6 Gy	11·1 (0–33·3)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
39 Gy	22·2 (11·1–33·3)	11·1 (0–33·3)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
Trial B					
50 Gy	11·1 (11·1–33·3)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
40 Gy	22·2 (11·1–33·3)	11·1 (0–33·3)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
Body image scale (0–30)					
Trial A					
50 Gy	3·0 (1·0–8·0)	3·0 (0–7·0)	3·0 (0–7·0)	2·0 (0–7·0)	2·0 (0–7·0)
41·6 Gy	4·0 (1·0–8·7)	2·0 (0–6·0)	2·0 (0–6·0)	2·0 (0–6·0)	2·0 (0–7·0)
39 Gy	4·0 (1·0–9·0)	2·0 (0–7·0)	2·0 (0–7·0)	2·0 (0–7·0)	2·0 (0–6·0)
Trial B					
50 Gy	3·0 (0–8·0)	2·0 (0–6·0)	1·0 (0–5·0)	1·0 (0–5·7)	1·5 (0–6·0)
40 Gy	3·0 (0–7·0)	2·0 (0–6·0)	1·0 (0–5·0)	1·0 (0–5·0)	1·0 (0–5·0)

Data are median (IQR). Higher scores indicate more symptoms or concerns.

Table 2: **Breast, arm, or shoulder symptoms and body image scale scores, according to radiotherapy regimen, over time from randomisation**

Table 1 shows characteristics of patients accrued into the quality-of-life study. More women received adjuvant chemotherapy (with or without tamoxifen) in trial A (38%, 427/1129) than in trial B (31%, 334/1079), consistent with differences in the composition of patients in the two trials (table 1). Most women had grade 1 or 2 tumours and were on endocrine therapy at the start of radiotherapy. In each regimen in trial A, a radiotherapy boost to the tumour bed was given to just under three-quarters of women who had completed breast-conserving surgery. In each regimen in trial B, about half of breast-conserving surgery patients received a boost.

Adherence to randomised treatment in each trial was very high (1110/1129 [98%] in trial A and 1065/1079 [99%] in trial B).[1,2] The proportion of completed quality-of-life questionnaires (based on the number of returned *vs* expected forms) was high, with 99% at baseline, decreasing only slightly over time to 91% at year 5.. Reasons for non-return of questionnaires included patient's withdrawal from the quality-of-life study, change of address, recurrence, and death, although most patients chose to remain in the study after a recurrence (figure 1). In terms of number of

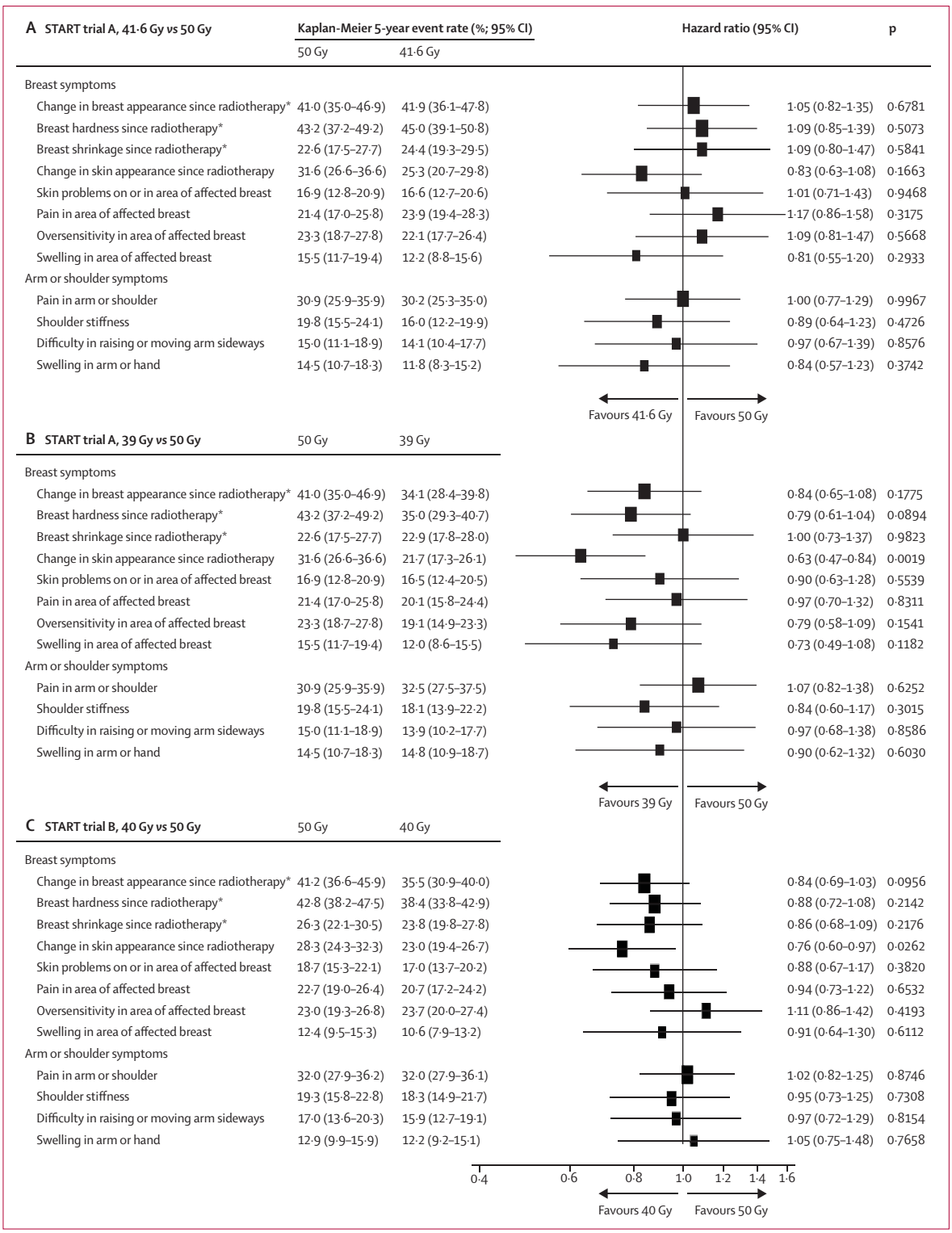

Figure 2: **Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimen**
Positions of squares in the forest plot show the estimate of the hazard ratio describing relative effect of the test schedule compared with control, with the 95% CI represented by horizontal lines. Squares to the left of the vertical line indicate when rates of adverse effects are lower in the test schedule compared with control; estimates to the right of the line indicate whether rates are higher in the test schedule. Size of squares is proportional to the precision of the estimate, with larger squares indicating greater precision. *In patients who had completed breast-conserving surgery only. (A) START trial A, 41·6 Gy *vs* 50 Gy. (B) START trial A, 39 Gy *vs* 50 Gy. (C) START Trial B, 40 Gy *vs* 50 Gy.

assessments completed per patient (including at baseline), approximately three-quarters of women returned all five booklets and the remaining quarter returned at least two. The number of women with a baseline and at least one follow-up assessment (denominators for the analysis) were 1080 in trial A and 1037 in trial B, representing 96% of the 2208 patients accrued into the quality-of-life study (figure 1).

With respect to breast, arm, and shoulder symptoms, the most frequently reported adverse effects in women who had completed breast-conserving surgery were breast hardness and overall change in breast appearance after radiotherapy (estimated 5-year rates 41% and 39%, respectively, with moderate or marked symptoms in both trials). In all radiotherapy regimens, the BR23 breast symptom subscale score declined significantly from baseline to 60 months (p<0·0001), but no significant differences between regimens were noted in trial A (p=0·5558) or trial B (p=0·8757; table 2). The rate of moderate or marked change in skin appearance after radiotherapy in all women (breast-conserving surgery and mastectomy) was significantly lower for the 39 Gy versus 50 Gy regimen in trial A (hazard ratio 0·63, 95% CI 0·47–0·84) and for the 40 Gy versus 50 Gy regimen in trial B (0·76, 0·60–0·97), whereas the 41·6 Gy and 50 Gy regimens in trial A did not differ significantly (0·83, 0·63–1·08; figure 2). Although no further significant differences were found, there was a similar pattern for other post-radiotherapy effects in the breast, with lowest rates of adverse changes in the 39 Gy regimen of trial A and the 40 Gy regimen in trial B, and similar rates in the 41·6 Gy regimen compared with 50 Gy (figure 2). Differences between regimens usually arose by 1 year after randomisation and then persisted.

Direct comparison of the 41·6 Gy and 39 Gy regimens in trial A provided some evidence of a radiation dose response. Lower rates for some endpoints were noted in the 39 Gy schedule (eg, breast hardness since radiotherapy, hazard ratio 0·73, 95% CI 0·56–0·95; oversensitivity in area of affected breast 0·72, 0·52–0·98; change in breast appearance since radiotherapy 0·79, 0·62–1·02; and change in skin appearance since radiotherapy 0·76, 0·56–1·03).

Pain in the arm and shoulder affected up to a third of patients over 5 years across regimens, and the 5-year rate of moderate or marked shoulder stiffness was about 20% (figure 2). The highest symptom subscale scores were present at baseline after which time they fell significantly (p<0·0001; table 2). Baseline arm and shoulder symptoms were associated with axillary surgery (p=0·0129 for arm or shoulder pain; p=0·0319 for arm or hand swelling) and breast-conserving surgery (p=0·0163 for arm or shoulder pain). Within-patient analysis of individual items at every timepoint showed that many arm or shoulder effects persisted from baseline (of 705 patients with moderate or marked arm or shoulder pain during follow-up, 282 [40%] had symptoms at baseline).

	Type of primary surgery		Radiotherapy boost*	
	Breast-conserving surgery (n=848)	Mastectomy (n=232)	Boost (n=611)	No boost (n=235)
Change in skin appearance since radiotherapy				
50 Gy	1	1	1	1
41·6 Gy	0·92 (0·68–1·25)	0·53 (0·28–0·99)	1·00 (0·71–1·41)	0·72 (0·38–1·35)
39 Gy	0·63 (0·45–0·88)	0·64 (0·34–1·17)	0·58 (0·39–0·86)	0·77 (0·41–1·46)
Skin problems on or in area of affected breast†				
50 Gy	1	1	1	1
41·6 Gy	1·02 (0·70–1·50)	0·90 (0·39–2·10)	1·16 (0·73–1·84)	0·75 (0·38–1·47)
39 Gy	0·87 (0·58–1·30)	1·07 (0·48–2·38)	0·85 (0·51–1·41)	0·87 (0·45–1·69)
Pain in area of affected breast†				
50 Gy	1	1	1	1
41·6 Gy	1·29 (0·92–1·82)	0·82 (0·42–1·61)	1·16 (0·78–1·73)	1·77 (0·90–3·48)
39 Gy	1·01 (0·70–1·45)	0·87 (0·45–1·69)	0·84 (0·55–1·28)	1·66 (0·81–3·37)
Oversensitivity in area of affected breast†				
50 Gy	1	1	1	1
41·6 Gy	1·14 (0·81–1·58)	0·87 (0·42–1·81)	1·00 (0·68–1·48)	1·56 (0·84–2·92)
39 Gy	0·79 (0·55–1·12)	0·81 (0·39–1·68)	0·70 (0·46–1·07)	1·06 (0·55–2·05)
Swelling in area of affected breast†				
50 Gy	1	1	1	1
41·6 Gy	0·87 (0·58–1·32)	0·40 (0·11–1·51)	0·83 (0·51–1·34)	1·05 (0·46–2·38)
39 Gy	0·68 (0·44–1·05)	0·98 (0·36–2·61)	0·60 (0·36–1·01)	0·96 (0·41–2·21)
Arm or shoulder pain†				
50 Gy	1	1	1	1
41·6 Gy	1·05 (0·79–1·39)	0·83 (0·47–1·47)	0·92 (0·65–1·29)	1·62 (0·93–2·84)
39 Gy	1·11 (0·83–1·48)	0·97 (0·56–1·69)	0·95 (0·68–1·33)	1·81 (1·01–3·24)
Shoulder stiffness†				
50 Gy	1	1	1	1
41·6 Gy	0·94 (0·65–1·37)	0·74 (0·37–1·46)	0·89 (0·58–1·38)	1·18 (0·55–2·49)
39 Gy	0·98 (0·67–1·41)	0·45 (0·20–0·99)	0·80 (0·51–1·24)	1·68 (0·81–3·44)
Difficulty in raising or moving arm sideways†				
50 Gy	1	1	1	1
41·6 Gy	1·16 (0·76–1·77)	0·61 (0·30–1·24)	1·12 (0·68–1·85)	1·29 (0·58–2·86)
39 Gy	1·15 (0·75–1·76)	0·61 (0·31–1·23)	1·09 (0·66–1·81)	1·32 (0·61–2·89)
Arm or hand swelling†				
50 Gy	1	1	1	1
41·6 Gy	0·77 (0·49–1·21)	1·09 (0·50–2·35)	0·56 (0·32–0·98)	1·45 (0·38–2·18)
39 Gy	0·92 (0·60–1·42)	0·88 (0·40–1·95)	0·88 (0·53–1·44)	0·89 (0·36–2·18)

Data are crude hazard ratio (95% CI). *Breast-conserving patients only; boost unknown for two women. †Results adjusted for baseline scores.

Table 3: **Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments, according to fractionation schedule, type of primary surgery, and boost in START trial A**

Arm and shoulder symptom subscale scores did not differ significantly between regimens (p=0·2071 for trial A and p=0·3101 for trial B; table 2). In trial A there was some evidence of fewer arm and shoulder adverse effects for the 41·6 Gy and 39 Gy regimens compared with 50 Gy, although these were not statistically significant. There were no consistent differences between the regimens in trial B (figure 2).

With respect to body image, 851 of 2117 (40%) women with relevant data reported moderate or marked concerns on at least one body-image item over 5 years of follow-up.

	Type of primary surgery		Radiotherapy boost*	
	Breast-conserving surgery (n=911)	Mastectomy (n=126)	Boost (n=470)	No boost (n=437)
Change in skin appearance since radiotherapy				
50 Gy	1	1	1	1
40 Gy	0·80 (0·63–1·03)	0·48 (0·20–1·16)	0·72 (0·52–1·01)	0·88 (0·61–1·27)
Skin problems on or in area of affected breast†				
50 Gy	1	1	1	1
40 Gy	0·86 (0·65–1·15)	2·26 (0·43–11·80)	0·76 (0·51–1·14)	0·97 (0·64–1·46)
Pain in area of affected breast†				
50 Gy	1	1	1	1
40 Gy	0·97 (0·74–1·26)	0·63 (0·22–1·79)	1·05 (0·72–1·53)	0·88 (0·59–1·30)
Oversensitivity in area of affected breast†				
50 Gy	1	1	1	1
40 Gy	1·18 (0·91–1·53)	0·55 (0·19–1·54)	1·33 (0·92–1·90)	1·05 (0·72–1·53)
Swelling in area of affected breast†				
50 Gy	1	1	1	1
40 Gy	0·89 (0·62–1·29)	4·18 (0·61–28·37)	0·94 (0·57–1·53)	0·80 (0·45–1·42)
Arm or shoulder pain†				
50 Gy	1	1	1	1
40 Gy	1·03 (0·83–1·29)	0·92 (0·47–1·80)	1·01 (0·74–1·36)	1·04 (0·75–1·44)
Shoulder stiffness†				
50 Gy	1	1	1	1
40 Gy	0·94 (0·70–1·25)	1·10 (0·47–2·58)	0·87 (0·58–1·31)	1·01 (0·66–1·54)
Difficulty in raising or moving arm sideways†				
50 Gy	1	1	1	1
40 Gy	0·99 (0·73–1·35)	0·79 (0·35–1·77)	0·90 (0·60–1·37)	1·03 (0·65–1·64)
Arm or hand swelling†				
50 Gy	1	1	1	1
40 Gy	1·12 (0·78–1·60)	0·65 (0·20–2·17)	0·65 (0·40–1·04)	2·29 (1·29–4·07)

Data are crude hazard ratio (95% CI). *Breast-conserving patients only; boost unknown for four women. †Results adjusted for baseline scores.

Table 4: **Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments according to fractionation schedule, type of primary surgery, and boost in START trial B**

The most typically reported moderate or marked concerns were feeling physically less attractive (496/2111 [23%]) and dissatisfaction with body (483/2112 [23%]). Body image scale summary scores were similar in all regimens over time (p=0·9990 for trial A and p=0·3405 for trial B; table 2). Analysis of individual item scores showed no significant differences between regimens. An improvement in body image scale scores was noted for all regimens over time compared with baseline (p<0·0001 in each trial; table 2).

In subgroup analyses, the relative effects of the randomised radiotherapy schedules on patient-reported symptoms did not vary significantly according to type of primary surgery (breast-conserving surgery or mastectomy) or whether or not a radiotherapy boost to the tumour bed was given (tables 3–5). Tests for interaction were not significant overall, and hazard ratios were similar in subgroups. The low numbers of patients and events in some subgroups limited the statistical power of these analyses.

Discussion

In our study, detailed self-assessments by patients in the START trials of normal tissue responses to breast radiotherapy over 5 years provided independent evidence that use of a lower overall radiotherapy dose in fewer larger fractions does not result in an increase in adverse effects or worse body image for most women, compared with the international standard regimen of 50 Gy in 25 fractions. Nevertheless, the experience by patients of breast and arm symptoms over 5 years represented chronic morbidity across all regimens. Breast pain has been implicated as a risk factor for poor long-term quality of life[18–20] and should be monitored by clinical teams, whereas functional symptoms such as shoulder stiffness could warrant early clinical attention. Breast and arm pain and oedema might have stronger associations than cosmesis with long-term quality of life[21] and, therefore, these are important outcomes to assess in clinical trials.

Little investigation has been done of self-reported breast, arm, and shoulder symptoms and functional outcomes after radiotherapy,[21,22] and thus our results make a potentially important contribution to the discussion of the effects of breast radiotherapy for informed consent. The findings also highlight the effect of previous surgery,[23,24] which should be taken into account when interpreting radiotherapy effects. The START quality-of-life study was designed to capture late effects of breast radiotherapy, because of concerns about hypofractionated regimens. Patients' reports of transient and short-term effects of radiotherapy have been reported, with limited effect on overall quality of life.[3,22,25,26] In future trials, well-defined, frequent, objective, and subjective assessments of relevant symptoms are desirable,[27,28] to establish the duration and functional outcomes of acute effects with more precision. We have reported adverse effects up to 5 years after radiotherapy, but we acknowledge that follow-up beyond 5 years is needed to assess further the pattern and severity of normal tissue effects, since they cannot be assumed to decrease over time, and some effects arise much later on. Follow-up in the START trials is ongoing, to assess the long-term effects of the fractionation schedules, although findings of the pilot study showed (with median follow-up of 10 years) that relative differences remained unchanged over time.[11] Interest in the late effects of specific treatments for breast-cancer survivors is growing, making clinical trials a suitable vehicle for gathering these data. The potential for continuing or late adverse effects adds to the importance of ensuring adequate clinical monitoring to offer women appropriate advice and support.

Breast changes that showed variation between radiotherapy regimens did not translate directly into differences in ratings of general body image concerns, suggesting that women did not experience breast changes in a way that affected their overall body image. This finding contrasts with the important effect on body image reported by these women before starting radiotherapy, when worse body image was associated with younger

age, having mastectomy, and chemotherapy.[13] The absence of variation in scores for body image between regimens might also indicate that the body image scale is designed to assess a range of concerns about overall attractiveness and appearance rather than specific aspects of breast appearance. Use of a radiotherapy boost and type of primary surgery have an adverse effect on cosmesis and patient-reported symptoms,[5,8,29] but they did not affect the comparison of the randomised schedules in the START trials.

In two other randomised controlled trials, researchers have compared the long-term effect of hypofractionated radiotherapy regimens at 5 years, but patient-reported normal tissue damage and cosmesis were not recorded.[11,30] The sensitivity of radiation dose to observer-rated breast symptoms and appearance was confirmed in the pilot study to the START trials,[11] and adverse changes in breast appearance from photographic assessments were significantly lower in the 39 Gy in 13 fractions regimen compared with the 50 Gy in 25 fractions control, with highest rates in patients who received 42·9 Gy in 13 fractions. By contrast, in a Canadian randomised trial comparing 42·5 Gy in 16 fractions against 50 Gy in 25 fractions, observer-rated cosmesis did not differ between schedules.[30]

The START trials comprise a well-defined cohort of patients, which is representative of women with early breast cancer in the UK. A strength of the quality-of-life assessments is the wide age and geographic range of participants and high levels of adherence to questionnaire completion over time. Individuals in the quality-of-life study were recruited from all parts of the UK, although London and the south of England were over-represented by comparison with annual distribution of new breast cancer cases for these areas (46% *vs* 35%, respectively).[31] Data for ethnic origin were not obtained in the START trials, so a statement about generalisability of our findings in that respect is not possible.

To our knowledge, our study is the first in which self-reported breast symptoms have identified differences over 5 years between alternative radiotherapy regimens in early breast cancer. Our findings accord with observer-rated photographic changes reported separately in the START trials,[1,2] which indicated that the difference between the two test dose levels in trial A in 2·0 Gy-fraction equivalents can be estimated to be 10%. Sensitivity of patients' self-ratings is highlighted by discrimination of this modest difference in dose intensity. The low rate of lymphatic radiotherapy given in the trials reduced the ability to detect differences in arm or shoulder symptoms between regimens. In our study, change in skin appearance was the outcome over 5 years that best discriminated between radiotherapy schedules, but other post-radiotherapy effects (eg, breast shrinkage and hardness) and breast symptoms showed comparable patterns.

Patients' perceptions of adverse effects are very important. We believe patient-reported outcomes should be used routinely in randomised trials of radiotherapy, where both the symptomatic impact of treatment and the extent of disruption to women's lives relating to length of treatment can affect quality of life.

In conclusion, considerable morbidity still arises due to effects on normal tissues of treatments for early breast cancer, and patients' self-assessments are important to ascertain the extent and duration of these effects. However, these ratings by patients in the START trials strengthen evidence in favour of hypofractionated regimens, with a potential for fewer adverse effects on the normal breast tissues. These findings have important implications for radiotherapy practice with quality-of-life benefits to patients.

	Type of primary surgery		Radiotherapy boost†	
	Breast-conserving surgery (n=704 [A]; n=775 [B])	Mastectomy (n=160 [A]; n=82 [B])	Boost (n=512 [A]; n=400 [B])	No boost (n=349 [A]; n=455 [B])
BR23 breast symptoms subscale (0–100)				
Trial A				
50 Gy	8·3 (0–25·0)	8·3 (0–20·8)	9·7 (0–25·0)	8·3 (0–16·7)
41·6 Gy	8·3 (0–16·7)	8·3 (0–25·0)	8·3 (0–16·7)	8·3 (0–16·7)
39 Gy	8·3 (0–16·7)	8·3 (0–22·9)	8·3 (0–16·7)	8·3 (0–25·0)
Trial B				
50 Gy	8·3 (0–16·7)	8·3 (0–16·7)	8·3 (0–16·7)	8·3 (0–16·7)
40 Gy	8·3 (0–16·7)	8·3 (0–16·7)	8·3 (0–16·7)	8·3 (0–16·7)
BR23 arm or shoulder symptoms subscale (0–100)				
Trial A				
50 Gy	11·1 (0–22·2)	11·1 (5·6–33·3)	11·1 (0–22·2)	11·1 (0–33·3)
41·6 Gy	11·1 (0–22·2)	11·1 (0–33·3)	11·1 (0–22·2)	11·1 (0–22·2)
39 Gy	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
Trial B				
50 Gy	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
40 Gy	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)	11·1 (0–22·2)
Body image scale (0–30)				
Trial A				
50 Gy	1·0 (0–5·0)	8·0 (2·2–15·5)	2·0 (0–6·0)	2·0 (0–8·0)
41·6 Gy	2·0 (0–7·0)	3·0 (0–8·0)	2·0 (0–7·0)	1·5 (0–7·0)
39 Gy	1·0 (0–5·0)	6·0 (1·0–11·0)	1·0 (0–4·0)	4·0 (0–9·0)
Trial B				
50 Gy	1·0 (0–5·0)	4·0 (1·0–9·5)	2·0 (0–5·5)	1·0 (0–6·0)
40 Gy	1·0 (0–5·0)	4·0 (0–7·0)	1·0 (0–6·0)	2·0 (0–5·0)

Data are median (IQR). Higher scores indicate more symptoms or concerns. *Subgroup analyses undertaken with all follow-up data in generalised estimating equation models, but only 5-year data are shown for simplicity of presentation. †Breast-conserving surgery patients only.

Table 5: **Breast, arm, or shoulder symptoms and body image scale scores at 5 years* according to radiotherapy regimen, type of primary surgery, and boost**

Contributors

PH designed the quality-of-life study, contributed to trial management and data interpretation and was a major contributor to writing of the report. JSH was primarily responsible for data analysis, contributed to data interpretation and was a major contributor to writing of the report. JM coordinated the quality-of-life study and helped to write the report. GS contributed to data interpretation and made comments on the report. JMB was responsible for the overall START trials, oversaw all statistical analyses, and made comments on the report. JRY (chief investigator for

the START Trials and Chair of the Trial Management Group) contributed to data interpretation and helped to write the report. All authors were members of the START Trial Management Group.

Conflicts of interest

The authors declared no conflicts of interest.

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